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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,887	HOGAN, KIRK	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106-191* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106-191* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on September 27, 2006 has been entered.

2. This action is in response to the papers filed September 27, 2006. Currently, claims 106-191 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. This action is made FINAL.

4. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 106-124, 126-191 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meet with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "two or more known genetic variations associated with two or more conditions".

However, Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalation anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases (abstract). Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided (page 471, col. 2). Quane also teaches that Arg615Cys is a substitution found in 3-5% of human MH families investigated (page 472, col. 1); Arg163Cys is a substitution found in 2-3% of MHS cases. Furthermore, three other rare mutations have been reported in the RYR1 gene which are in three isolated MHS and/or CCD cases. Quane teaches that patients which have not been indicated as MH normal should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia. Misdiagnosis of MHS individual as MHN can be lethal if such a patient is exposed to triggering agents (page 474, col. 1). Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col 2).

Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular

metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent. SC and mivacurium are potentially toxic in people with BchE deficiency. AAS teaches that the principles of molecular biology tests and their application to BchE variants are well illustrates and anesthesiologists need to keep up to date about these applications. AAS also teaches that other hereditary conditions of special interest to anesthesiologists, such as malignant hyperthermia, may be diagnosed by similar methods in a few years (page 141).

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80).

Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of CYP2D gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that "inherited differences in drug-metabolizing capacity are generally monogenic traits and their

influence on the pharmacokinetices and pharmacologic effects of medications is determined by their importance for the activation or inactiviation of drug substrates (page 487, col. 2). Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1).

Poort et al (herein referred to as Poort) teaches an 20210 AG gentoype of the prothrombin gene which is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most

common hereditary risk factor for thrombosis. Poort teaches two genetic markers which are associated with thrombosis.

Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays. Hoon teaches using multiple markers provides increased sensitivity (abstract). Hoon teaches that marker combinations may be developed, which are particularly sensitive to the effect of therapeutic regimens on disease progress such that patients may be monitored (col. 4, lines 65-68). In a particular example, Hoon demonstrates that number of markers was studied and that using four markers was significantly better than a single marker alone (col. 21).

Additionally, Hacia teaches mutational analysis using oligonucleotide microarrays. Hacia teaches that arrays of 1,480 oligonucleotide probes were designed to detect 37 known mutations, probes were spotted on surfaces to detect mutations in HBB, and BRCA1. Hacia teaches that arrays of 135,000 probes were used to interrogate the entire 16.6kb human mitochondrial genome from ten samples (page 44, col. 1). Chips have also been used for the simultaneous genotyping of 500 markers (page 45, col. 1). Hacia teaches that chips allow for unprecedented throughput in mutational analysis with a high degree of accuracy (page 46, col. 2). Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the

patient to anesthetics, as taught by Miller, to determine whether they were at risk of MH, a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Quane, Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, Evans or Poort . Miller teaches that it is routine to sample patients blood to analyze the blood for abnormalities including hematocrit levels. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). Quane provides three examples of common mutations within the RYR1 gene which are associated with MH and which trigger MH syndrome during anesthesia, and potentially death. Quane specifically states that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" (page 471, col. 2). AAS teaches that SC and mivacurium are potentially toxic in people with BchE deficiency. La Du et al teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine and the variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches that codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and

fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Additionally, Port teaches that factor V Leiden is the most common hereditary risk factor for thrombosis and two genetic markers which are associated with thrombosis.

Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within the RYR1, CYP2D6, Prothrombin, BCHE genes for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition of MH to avoid any fatal reaction to the anesthesia, for example. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for genetic abnormalities within RYR1. The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics.

Moreover, given the teachings of Hoon and Hacia that sampling multiple markers provides increase sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery. Therefore, the skilled artisan would have additionally analyzed a patient for a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans or Poort. Given the

state of the art with relation to known markers and detecting the markers as indicative of certain disease which either trigger episodes when exposed to anesthetics, or are poor metabolizers or potentially cause thrombosis are well known. The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any of the known genes for known mutations which are associated with known conditions for the expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed, to screen individuals prior to surgery for several genetic markers which are indicative of any number of conditions which are caused by anesthesia or are a result of anesthesia. Hacia teaches that large numbers of probes are placed on arrays for the express benefit of high-throughput mutational analysis with a high degree of accuracy (page 46, col. 2). The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these

conditions to arise. Specifically, detection of RYR1 polymorphisms which are associated with MH would indicate to the anesthesiologist that drugs which trigger the episodes should be avoided. Moreover, codeine should be administered with care to individuals having certain BchE mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patients genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

With respect to the claims drawn to invasive and non-invasive surgery, anesthesia and codine, for example are administered routinely in each of these situations.

With respect to the claims drawn to specific numbers of markers, for example 5 and 10 or more mutations, the skilled artisan would be motivated to screen makers which were well known at the time of the art simultaneously or in tandem for the benefits of providing the most complete amount of information possible. Hacia specifically teaches that arrays to detect mutations of approximately 500 were known in the art at the time the invention was made.

Response to Argument

The Response traverses the rejection. The response filed September 27, 2006, January 2004, July 23, 2004 and the brief filed September 21, 2005 asserts that the cited art fails to establish prima facie obviousness. The claims are drawn to testing two or more nucleic acid markers in two or more genes associated with two or more

conditions and selecting a course of action based on the information from the profile. The Response asserts that the Board and the Examiner have failed to establish a prima facie case of obviousness. As specifically provided by 706.07(h), "In addition to the res judicata effect of a Board of Patent Appeals and Interferences decision in an application (see MPEP § 706.03(w)), a Board decision in an application is the "law of the case," and is thus controlling in that application and any subsequent, related application." The applicant had the opportunity to appeal any Board decision from which they were dissatisfied. The response raises many issues and concerns with regard to the Board and the Examiner's position. It is noted that as provided in 35 U.S.C. 141. "An applicant dissatisfied with the decision in an appeal to the Board of Patent Appeals and Interferences under section 134 of this title may appeal the decision to the United States Court of Appeals for the Federal Circuit. By filing such an appeal the applicant waives his or her right to proceed under section 145 of this title."

With respect to the newly added method step of selection a perioperative course of action based on information from the genomic profile, this limitation was previously presented in a "for use" clause and was afforded weight. Thus re-writing the claim in a different format does not change the position of the Examiner or the Decision on Appeal. It would have been obvious once the genomic profile was selected, that a perioperative course of action based on the information from the profile would be followed. It is clear that Claim 86 from appeal already positively recited this additional method step and was affirmed by the Board.

With respect to Claim 149, the newly added limitations are all directed to obtaining consent, and distributing the results according to patient's preference. Miller specifically obtains consent based upon the consent form and signature on page 1325 of Miller. Furthermore, the results of the analysis that the patient is receiving would be distributed to those individuals who could make an informed decision to the course of action. These individuals would be according the patience preference.

With respect to Claim 187-188, Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded.

Thus, for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

New Matter

6. Claim 125 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "TNFalpha and TNFbeta" are included. The amendment does not point to any particular support for these two genes. Instead the specification describes discusses genes in Tables 1-4. It is noted that the CIP application has added the two TNF genes, but this parent application does not refer to TNFalpha or TNFbeta. This description does not support TNFalpha and TNFbeta. The

concept of markers within "TNFalpha and TNFbeta" does not appear to be part of the originally filed invention. Therefore, "TNFalpha and TNFbeta" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

7. Claim 125 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) as applied to 106-124, 126-191 above and further in view of the specification (Tables 1-4).

Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia do not specifically teach profiling for each of BchE, CYP2D6, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, CTP2, TNFA and TNFB.

The instant specification teaches markers in each of these genes which are associated with various operative related disorders. The specification clearly illustrates genes and mutations which are associated with the particular mutations. The response filed March 26, 2001 specifically illustrates that the invention does not claim discovery of newly identified DNA sequences (page 7).

Therefore, it would have been obvious in view of the teachings of Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia to include any number of genes on the array of Hacia for the highthroughput analysis of operatives complications.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 126 and 186 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 26 is directed to a method further comprising using the profile for selection of conditions which appear to be already present in step (c) of the newly added Claim.

B) Claim 186 is indefinite because the method relies on a kit. It is unclear how the assay comprises a kit. It is unclear whether the assay comprises using a kit or whether the assay is intended to be limited to a kit. Clarification is required.

Conclusion

9. This is a RCE of applicant's earlier Application No. 09/613,887. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL**

even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

Jeanine Goldberg
Primary Examiner
December 7, 2006